REMARKS

Claims 1-3, 6, 32-34, 47, 50, 54, 57, 58, 61-74, 76-80, 82-101 and 108-110 are pending in this application. Claims 1, 32-34, 54, 57, 58, 61, 62, 68, 69, 71, 82, 83, 94, 99 and 108-110 are amended, and Claims 8-10, 12, 22, 24, 31, 55, 56, 102-107 and 111-114 are cancelled. The claim amendments are for clarity/consistency of language, to more distinctly point out the nature of what is claimed and/or to provide proper antecedent basis. No new matter is added.

In the interest of advancing the application to allowance, independent Claims 1 and 99 are amended herein to recite a compound (Claim 1) or an isolated polypeptide (Claim 99) containing a peptide or protein that is a human or bacterial sialidase or an active portion thereof having sialidase activity that cleaves α(2,3)-Gal and/or α(2,6)-Gal linkages, and a peptide or protein that binds to a glycosaminoglycan (GAG) on the surface of a target cell, where the peptide or protein that binds to a GAG contains the GAG-binding amino acid sequence of: human platelet factor 4 (SEQ ID NO:2), human interleukin 8 (SEQ ID NO:3), human antithrombin III (SEQ ID NO:4), human apoprotein E (SEQ ID NO:5), human angio-associated migratory protein (SEQ ID NO:6), or human amphiregulin (SEQ ID NO:7). Basis for these amendments can be found in the claims as originally filed and in the specification, for example, at page 21, lines 3-30 and in Example 4 beginning at page 40. The cited sections also provide basis for the amendment of dependent claims 62, 83, 94 and 110 to recite an additional bacterial sialidase, the "*Arthrobacter ureafaciens*" sialidase.

Withdrawn method claims 50, 54, 57, 58 and 82-94, directed to non-elected subject matter, are retained for possible rejoinder upon allowance of product claims deemed allowable.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

Claims 1-3, 6, 8-10, 12, 22, 24, 31-34, 47, 61-74, 76-80 and 94-110 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description. The Examiner alleges that the specification provides an adequate written description only for compounds and polypeptides containing a therapeutic domain having the human sialidase sequence of SEQ ID NO:8 or SEQ ID NO:9, and an anchoring domain having a GAG-binding sequence of SEQ ID NOS: 2-7 (page 4, last paragraph of the Office Action). He states that the scope of the genus of compounds containing a peptide or protein having sialidase activity that cleaves α(2,3)-Gal and/or α(2,6)-Gal linkages and a peptide or protein that binds to a

glycosaminoglycan (GAG) on the surface of a target cell includes many members with widely differing structural, chemical and physicochemical properties, and there allegedly is no definition of the common structural features and biological functions possessed by members of the "therapeutic domain" and members of the "anchoring" domain.

The Examiner refers to arguments made by Applicant in the Response filed September 8, 2008, in which Applicant cited *Invitrogen Corporation v. Clontech Laboratories, Inc.* (429 F.3d 1052 (Fed. Cir. 2005)) for the proposition that the disclosure of even a single embodiment of a recombinant gene encoding a mutant protein, when coupled with the knowledge of homologs in the prior art, can satisfy the written description requirement for even broad claims to proteins. In response to those arguments, the Examiner states that unlike the example in the *Invitrogen* case, Applicant's compound as recited in the claims is not defined by its source. He further notes that while individual sequences of the various domains may be well-defined or well-known in the art, the selection of appropriate domains used in specific constructs is crucial to the functioning of the compounds, and the specification allegedly is inadequately descriptive of the genus of such constructs embraced by the claims.

Reconsideration of this rejection is requested in view of the amendments herein and the following remarks. The rejection is rendered moot with respect to Claims 8-10, 12, 22, 22, 24, 31 and 102-107, which are cancelled herein.

Analysis

In the interest of advancing the application to allowance, the claims are amended herein to specify that the compound or isolated polypeptide contains a peptide or protein that is a sialidase or active portion thereof, wherein the sialidase is a human or bacterial sialidase having sialidase activity that cleaves α(2,3)-Gal and/or α(2,6)-Gal linkages, and a peptide or protein that binds to a GAG and contains the GAG-binding amino acid sequence of: human platelet factor 4 (SEQ ID NO:2), human interleukin 8 (SEQ ID NO:3), human antithrombin III (SEQ ID NO:4), human apoprotein E (SEQ ID NO:5), human angio-associated migratory protein (SEQ ID NO:6), or human amphiregulin (SEQ ID NO:7).

The Examiner acknowledges that the specification describes compounds having a sialidase of SEQ ID NO:8 (the human sialidase NEU2) or SEQ ID NO:9 (the human sialidase NEU4), and a GAG-binding protein or peptide that includes any one of SEQ ID NOS: 2-7.

Applicant submits that with respect to the sialidase, the description in the specification evidences Applicant's appreciation and possession, not only of human sialidases

NEU2 and NEU4 of SEQ NO:8 or SEQ ID NO:9, respectively, but of human sialidases *in general* as components of the claimed compounds and isolated polypeptides. As noted in the specification, the human sialidases can inhibit pathogenic infection by blocking sialic acid receptor – mediated pathogen entry. The specification also describes bacterial sialidases as being among the candidates of choice for making the claimed compounds and polypeptides.

The specification provides descriptions of many known bacterial and human sialidases, citing to references and Genbank Accession numbers for their sequences. At page 21, lines 3-30 and page 42, line 1 to page 45, line 27, the specification describes how bacterial sialidases, such as those from *Arthrobacter ureafaciens* sialidase, *Clostridium perfringens* sialidase, *Actinomyces viscosus* sialidase, *Vibrio cholerae* sialidase and *Micromonospora viridifaciens* sialidase, and active portions of these sialidases, are useful in the claimed compounds because they can cleave α(2,3)-Gal and/or α(2,6)-Gal receptor sialic acids, thereby preventing and/or treating infection by pathogens whose mode of infection involves binding to sialic acid receptors. The cited sections also describe human sialidases as suitable by virtue of their similar substrate specificity, and further describe and reference the cloning and sequencing of four human sialidases: NEU1, NEU2, NEU3 and NEU4. Clearly, at the time the present application was filed, many human and bacterial sialidases were known and fully characterized, not just the ones whose sequences are set forth in SEQ ID NOS. 8 and 9. The cited sections further describe linking the (human or bacterial) sialidases, or active portions of the sialidases, to GAG-binding proteins or peptides that include any one of SEQ ID NOS: 2-7. The same sections also describe how sialidases across a wide variety of species (bacterial, human, viral, fungal, *etc.*) share a similar structural fold, especially in the catalytic region. Given this characterization, and the many known human and bacterial sialidases listed in the specification, there is no question that Applicant appreciated and described the common structural features and biological functions that characterize a suitable bacterial or human sialidase, or active portion thereof, for use in the compounds and polypeptides claimed herein.

The specification also describes the construction and optimization of fusion proteins containing a sialidase from bacterial and human sources and a GAG-binding protein or peptide (page 4, lines 26-30; page 21, line 23 to page 22, line 11; Example 6). Examples 4 and 5 describe how to clone, express, purify and select suitable sialidases, and assay for their activity. The specification describes in detail the various configurations in which the two domains (sialidase and GAG-binding), with or without a linker between them, can be

arranged (page 9, line 13 to page 11, line 31). Given this characterization of compounds containing sialidases and GAG-binding proteins or peptides in the specification, one can readily use this information to identify and construct other fusion proteins having similar properties.

Applicant submits that the present claims in fact are very similar to those of the *Invitrogen* case. In *Invitrogen*, the court held that the description of a single sequence of a mutant reverse transcriptase lacking RNAseH activity (derived from MMLV, a retrovirus) satisfied the written description requirement not only for mutant reverse transcriptases with reduced RNAse H activity from retroviruses, but also for the mutant enzymes from a variety of other sources including yeast, *Neurospora*, *Drosophila*, primates and rodents.[1] This conclusion was based on the fact that the sequences of several reverse transcriptase genes were known and it was known that several members of the reverse transciptase gene family shared significant homology. Similarly, the present claims are directed to compounds and isolated polypeptides in which a human or bacterial sialidase, or active portion thereof, is linked to a particular, known sequence of a GAG-binding protein or peptide that is selected from among six specific sequences. The sequences of several human and bacterial sialidases were known as of the application's priority date, as was their common substrate specificity.

The detailed description in the specification of human and bacterial sialidases, and GAG-binding amino acid sequences, the extensive knowledge in the art regarding the same, and the description in the specification of compounds containing a human or bacterial sialidase and a GAG-binding protein or peptide that includes any one of SEQ ID NOS: 2-7, clearly evidences Applicant's possession of the subject matter as claimed. Therefore, Applicant submits that the written description requirement is satisfied.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH (ENABLEMENT)

Claims 1-3, 6, 8-10, 12, 22, 24, 31-34, 47, 61-74, 76-80 and 94-110 are rejected under 35 U.S.C. §112, first paragraph, as not being enabled for their full scope. In particular, the Examiner alleges that the specification, while being enabling for a compound or composition comprising a compound consisting of a "therapeutic domain" selected from among SEQ ID NO:8 and SEQ ID NO:9, and an "anchoring domain" selected from among the GAG-binding

[1] See also *Capon v. Eshhar v. Dudas*, 418 F.3d 1349 (Fed. Cir. 2005), in which the Court of Appeals for the Federal Circuit held that claims drawn to chimeric genes containing a sequence encoding a single-chain variable domain of an antibody and a sequence encoding the cytoplasmic, transmembrane and extracellular domains of a lymphocyte signaling protein, were adequately described in light of a few examples in the specification and the extensive knowledge in the art regarding the sequences and structures of each of the encoded domains.

domains of SEQ ID NOS: 3, 4, 5 or 7, does not reasonably provide enablement for a composition containing anchoring and/or therapeutic domains of "undetermined structure and function for preventing pathogenic infection."

The Examiner further alleges that the disclosure is not sufficiently enabling for the full scope of the claims, which as pending encompass an "extremely large number" of fusion constructs. He states that the dependent claims 2-3, 6-10, 12-14, 22, 24, 31-34, 47, 61-79 and 94-98 identify specific target cells, therapeutic domains and anchoring domains, but allegedly "lack the complete structure of the compound in any single claim nor specify having a defined function with respect to a specific pathogen…"

With respect to pharmaceutical composition claims 47, 72, 73 and 76-79, it again is alleged that the specification is only enabling for pharmaceutical compositions of compounds in which the "therapeutic domain" (*i.e.*, the sialidase) is selected from among SEQ ID NO:8 and SEQ ID NO:9, and the "anchoring domain" is selected from among the GAG-binding domains of SEQ ID NOS: 3, 4, 5 or 7. The Examiner further alleges that the specification provides no teaching, nor is there any data, showing that the claimed fusion proteins are "associated with any of the known diseases or disorders or infections or can be treated or prevented" by administering the fusion constructs. He cites Applicant's own work (Malakhov et al., *Antimicrob. Agents Chemother.*, 1470-1479 (2001)) and states that while a specific fusion construct of a sialidase catalytic domain and a human amphiregulin GAG-binding domain may have broad spectrum activity against influenza viral infections, there is no reason to believe that any sialidase fusion construct will be effective in controlling any viral infection or have any other effective use.

Reconsideration of this rejection is respectfully requested in view of the amendments herein and the following remarks. The rejection is rendered moot with respect to Claims 8-10, 12, 22, 22, 24, 31 and 102-107, which are cancelled herein.

Analysis

Compound / Isolated Polypeptide Claims

The Examiner alleges that it is unpredictable which of the constructs produced as taught by the specification will actually have a therapeutic effect. Applicant respectfully submits that this is not the proper standard for enablement. To satisfy the requirement of enablement, a claim does not have to explicitly exclude every conceivable inactive variant. *In re Application of Dinh-Nguyen*, 492 F.2d 865 at 858-9 (CCPA 1974). Rather, the question

is whether by following the teachings of the application, one of skill in the art can practice what is claimed with perhaps routine, but not undue, experimentation.

The present claims specify a compound or isolated polypeptide containing a peptide or protein that is a human or bacterial sialidase or active portion thereof having sialidase activity that cleaves α(2,3)-Gal and/or α(2,6)-Gal linkages; and a peptide or protein that binds to a glycosaminoglycan (GAG) on the surface of the target cell, where the peptide or protein contains a GAG-binding peptide selected from among any one of SEQ ID NOS: 2-7. The teachings of the specification, when combined with the knowledge of those of skill in the art regarding the particular GAG-binding domains of SEQ ID NOS: 2-7, and the sequence, structural and functional characterization of human and bacterial sialidases, including their common features and substrate specificities, is so extensive as to render the specification adequately enabling for compounds and isolated polypeptides containing these known domains.

The specification teaches a number of known bacterial and human sialidases, their sequences and their substrate specificities that confer the ability to prevent or treat sialic acid receptor-mediated infection by a pathogen. The specification also teaches linking a bacterial or human sialidase to the GAG-binding proteins or peptides that include any one of SEQ ID NOS: 2-7 (page 21, lines 3-30; Example 4 beginning at page 40). In addition, Examples 4 and 5 of the specification teach how to clone, express, purify and assay human and bacterial sialidases for selection of the optimal candidates for preparation of fusion constructs with a GAG-binding protein or peptide. Example 6 teaches how to construct, optimize and test sialidase/GAG-binding peptide fusion constructs. Thus, by following the teachings of the specification, one can: (1) make a variety of compounds containing a human or bacterial sialidase or active portion thereof and a GAG-binding protein or peptide that includes any one of SEQ ID NOS: 2-7, and (2) test them in standard infectivity assays (as described, *e.g.*, in Example 2) for their ability to prevent or treat infection by a pathogen.

Pharmaceutical Composition Claims

With regard to the pharmaceutical composition claims 47, 72, 73, and 77-79, the Examiner asserts that the lack of a working example demonstrating the therapeutic efficacy of one or more exemplary fusion proteins is evidence of lack of enablement. The Office Action further cites Malakhov et al., of record in this case and discussed in the Response filed September 8, 2008, as allegedly providing no "reason to believe" that any sialidase fusion

construct other than the specific fusion construct disclosed in the publication will be effective against influenza or any other viral infection.

Applicant respectfully disagrees. The question that goes to enablement of the claimed pharmaceutical compositions is whether the specification provides sufficient guidance for one of skill in the art to be able to use the compositions to prevent or treat a pathogenic infection. As discussed below, the specification has provided ample teachings to be able to do so. No actual working examples are necessary. In addition, Malakhov et al. demonstrates that the claimed pharmaceutical compositions are operative in their intended therapeutic use as demonstrated by their activity against an exemplary pathogen, influenza. Thus, Malakov et al. far from providing no "reason to believe" that other sialidase fusion constructs will be effective, actually supports Applicant's assertion that other sialidase fusion constructs will be effective. The Examiner has not given any reason for concluding that other molecules within the claims will not be effective.

(1) Teachings of the Specification and the Knowledge of those of Skill in the Art

A number of bacterial and viral pathogens are known to use sialic acid receptors on target cells to bind and/or infect the target cells. As taught by the specification and as known to those of skill in the art, such pathogens include influenza virus, parainfluenza virus, paramyxoviruses, coronaviruses, rotaviruses, Sendai virus, reovirus, polyoma viruses and *Pseudomonas aeruginosa*. The specification teaches how compounds containing: (a) a bacterial or human sialidase or active portion thereof having sialidase activity that cleaves α(2,3)-Gal and/or α(2,6)-Gal linkages of sialic acid receptors on a target cell; and (b) a GAG-binding protein or peptide containing one of SEQ ID NOS: 2-7 that anchors the sialidase to the target cell, can prevent the binding and entry of pathogens that use sialic acid receptors to enter and infect the target cell (specification at page 20, lines 28-29; page 22, lines 12-18; page 13, lines 10-15; page 21, line 23 to page 22, line 11). The specification teaches how to measure the sialidase activity of these compounds, and how to test them in infectivity assays. There is no reason why, given these teachings and the knowledge of those of skill in the art, one would not be able to obtain, without undue experimentation, therapeutically effective pharmaceutical compositions of the compounds.

(2) Compounds containing an active portion of a *Bacterial* Sialidase linked to a human amphiregulin GAG-binding domain (SEQ ID NO:7)

Furthermore, in the Response filed September 8, 2008 in connection with the above-captioned application, Applicant provided publications ((Malakhov et al., *Antimicrob. Agents*

Chemother., 1470-1479 (2001); Belser et al.., *J. Infect. Dis.*, 196:1493-1499 (2007)) demonstrating that a compound containing an active portion of a bacterial sialidase (a catalytic domain of *Actinomyces viscosus* sialidase having sialidase activity that cleaves α(2,3)-Gal and α(2,6)-Gal linkages) linked to the human amphiregulin GAG-binding domain (SEQ ID NO: 7), when tested in cell-based and animal-based models for its activity against an exemplary pathogen, influenza virus, showed a preventative and therapeutic effect against a number of influenza viral strains, including the highly virulent lethal avian influenza virus, H5N1. The compound used in the Malakhov et al. and Belser et al. studies is claimed in a related application, U.S. Application Serial No. 10/939,262.

(3) Compounds containing a *Human* Sialidase linked to a human amphiregulin GAG-binding domain (SEQ ID NO:7)

The enclosed Declaration of Fang under 37 C.F.R. §1.132 demonstrates that an exemplary compound containing a human sialidase (NEU2) linked to a GAG-binding peptide of SEQ ID NO: 7: (a) has sialidase activity and cleaves the sialic acid receptors from target cells used in the assays; and (b) protects the target cells from being infected by a variety of strains of influenza virus.

A detailed in the Declaration, a polypeptide, AR-G_{4s}-Neu2, ("Compound 1") containing human sialidase NEU2 linked *via* a G_{4s} linker (4 glycines, followed by a serine) at its C-terminus to the GAG-binding peptide of human amphiregulin was prepared. The ability of Compound to remove sialic acid from cell surfaces was tested and confirmed.

As also detailed in the Declaration, Compound 1 was tested for its ability to protect cells against an influenza virus challenge. MDCK cells were treated for 2 hrs with Compound 1. The cells were then challenged with a broad selection of human influenza viruses at MOI 0.1 for 1 hr (highlighted in bold in Table 1 of the Declaration), and the viral titer was compared to control cells not exposed to Compound 1 prior to the viral challenge.

These studies showed that Compound 1 conferred protection against all the tested influenza strains. Thus, the Declaration demonstrates that a compound containing a human sialidase linked to a GAG-binding domain can be administered as a pharmaceutical composition to protect target cells from influenza virus.

In light of the above experimental evidence, Applicant respectfully submits that the composition claims 47, 72, 73 and 77-79 of a compound containing a bacterial or human sialidase or active portion thereof with sialidase activity that cleaves α(2,3)-Gal and/or α(2,6)-Gal linkages, are operative in their intended use as pharmaceuticals.

THE REJECTION UNDER 35 U.S.C. §101 (NON-STATUTORY SUBJECT MATTER)

Claims 99-110 are rejected as directed to non-statutory subject matter because naturally occurring proteins, in the absence of the hand of man, are regarded as such. In response to Applicant's previous response pointing out that the claimed polypeptides are made by man and do not occur in nature, the Examiner rebuts that "compound proteins and gene clusters" do occur in nature. The Examiner asks that Applicant address this rejection by amending the claims to recite "isolated" polypeptide or a "fusion protein."

Without conceding the propriety of this rejection, the rejected claims are amended herein to recite "isolated," thereby rendering the rejection moot.

THE REJECTION OF CLAIMS 1-3, 6-10, 12-14, 22, 24, 31-34, 47, 61-79 AND 94-98 UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE-PATENTING

Claims 1-3, 6-10, 12-14, 22, 24, 31-34, 47, 61-79 and 94-98 are provisionally rejected under the judicially created doctrine of obviousness-type double-patenting over claims 141-147, 149, 151, 162-169 and 171 of co-pending Application Serial No. 10/939,262. Without addressing its merits or conceding its propriety, this rejection will be addressed as appropriate upon indication that there is allowable subject matter in one or both applications.

CONCLUSION

It is believed that the claims are in condition for allowance. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date:22 December 2009

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